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iREVIEWS

STATE-OF-THE-ART PAPER

CME

Cardiac Magnetic Resonance in Hypertrophic Cardiomyopathy

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Cardiac Magnetic Resonance in Hypertrophic Cardiomyopathy

Hypertrophic cardiomyopathy is a complex genetic cardiovascular disorder with substantial variability in phenotypic expression and natural progression. Recent research demonstrates the incremental utility of cardiac magnetic resonance in the diagnosis, therapeutic planning, and prognostication of this disease. The increasing incorporation of multimodality imaging of hypertrophic cardiomyopathy in clinical practice will continue to improve our understanding of the subtle morphologic differences and their prognostic implications. (J Am Coll Cardiol Img 2011;4:1123–37) © 2011 by the American College of Cardiology Foundation

Hypertrophic cardiomyopathy (HCM) is the most common genetic cardiovascular disorder, with an estimated prevalence of 1:500 in the general population (1,2). It is typically inherited as a Mendelian autosomal dominant trait, with over 600 mutations identified in sarcomeric genes (3,4). Recently, mutations in genes encoding Z-disc proteins and proteins involved in calcium regulation have also been implicated (5). This genetic diversity together with modifier genes and environmental factors form the basis of its phenotypic heterogeneity.

Symptoms of HCM can develop from childhood and include exertional dyspnea, chest pain, presyncope, and syncope, resulting from differing combinations of dynamic left ventricular outflow tract (LVOT) obstruction, left ventricular (LV) diastolic and systolic dysfunction, and supraventricular/ventricular arrhythmias. Although many patients remain asymptomatic with a benign natural history, sudden cardiac death (SCD) might be the initial manifestation in many otherwise asymptomatic or mildly symptomatic young people (1,6). Current risk prediction models include prior SCD, family history of SCD, unexplained syncope, spontaneous sustained ventricular tachycardia, nonsustained ventricular tachycardia on continuous electrocardiography (ECG) monitoring, abnormal exercise blood pressure, and LV thickness ≥30 mm (6). Such prediction models are far from perfect for several reasons. Although a low risk of SCD has been demonstrated in those without the aforementioned risk markers (7), the negative predictive value is likely overestimated, because not all cases of SCD are captured in retrospective studies. Conversely, the positive predictive value of individual risk factors is low, with the exception of prior aborted SCD and spontaneous sustained ventricular tachycardia (8). The concern remains that, if implantable cardioverter defibrillators (ICDs) were inserted in all patients with any "high-risk" feature, the incidence of device complications would surpass the potential benefits.

Emergence of Cardiac Magnetic Resonance in HCM

Traditionally, the diagnosis of HCM relies upon clinical assessment and transthoracic echocardiography (TTE) to identify features such as left ventricular hypertrophy (LVH), systolic anterior motion of the mitral valve, and LVOT obstruction. In many clinical scenarios, technical limitations of echocardiography and heterogeneous phenotypic expression made such evaluation difficult, and cardiac magnetic resonance (CMR) has emerged as a useful adjunctive imaging modality to complement routine TTE (9). CMR is unique in its high spatial and temporal resolution with excellent contrast between blood pool and myocardium, without limitation of either imaging window or imaging plane. Late gadolinium enhancement (LGE) sequences enable the identification of myocardial fibrosis, which is associated with poor outcome (10–14). In our center and many others, CMR imaging is routinely performed in all new patients with suspected or known HCM as part of a comprehensive workup that also includes TTE with provocative maneuvers, exercise stress echocardiography, and transesophageal echocardiography (TEE) in select cases. Indeed, comprehensive CMR in the diagnostic workup of HCM is considered an appropriate use of technology (15,16). Although definitive cost-effectiveness data are unavailable, data are likely to be available in specific clinical scenarios where CMR aids in further refinement of the current strategies of diagnosis, screening, treatment, and prognosis. Table 1 summarizes

the details and limitations of the typical CMR study for HCM.

In this review article, we discuss the role of CMR in the diagnosis, treatment, and prognosis of HCM, with a focus on the complementary value of CMR in relation to standard imaging modalities, and we examine some of the emerging roles of CMR.

CMR and Diagnosis

The phenotypic heterogeneity of HCM is well-recognized. This is further complicated because not all patients with LVH have HCM, whereas HCM-like pathophysiology with dynamic LVOT obstruction can be observed without LVH, in a subgroup of patients with mitral valve and/or papillary muscle abnormalities. Figure 1 summarizes the diagnostic challenges faced by clinicians in both established and suspected HCM. Figure 2 highlights the areas where CMR potentially has incremental utility. Although a more comprehensive algorithm detailing the step-by-step diagnostic approach in HCM has been detailed elsewhere (17), a simplified approach to the differential diagnosis of HCM has been outlined in Figure 3. CMR enables the precise characterization of subtle disease phenotypic variations (Figs. 4, 5, 6, and 7, Online Videos 1, 2, and 3), especially important for characterizing LVOT, papillary muscle, subvalvular anatomy, and diagnosing of atypical HCM. High image quality and tissue characterization accurately identify the various conditions that mimic the morphological appearance of HCM (Figs. 8 and 9, Online Videos 4 and 5). Reproducible volume and mass quantification might also identify at-risk individuals with a family history of HCM and can be used to screen for pre-clinical disease.

Disease characterization: LVOT, papillary muscle, and subvalvular anatomy. Resting or provocable LVOT obstruction is present in 70% of cases and is an important manifestation of HCM (18). It relates to the complex anatomical relationships between the septum, LVOT, mitral valve, and papillary muscles. In the majority of HCM patients, septal hypertrophy leads directly to LVOT obstruction (Fig. 4, Online Video 1). However, some present with hypertrophy without obstruction, whereas others present with dynamic LVOT obstruction and minimal septal hypertrophy. The latter is likely due to a variety of papillary muscle and subvalvular abnormalities (19) (Fig. 5, Online Video 2). Such complexity highlights the importance of accurate anatomical assessment. TTE and TEE are the current standards in assessing LVOT anatomy and flow profile. The main advantage of CMR is in identifying the anatomy of the septal-systolic anterior motion contact and subvalvular apparatus. Isolated or concomitant mid-ventricular obstruction related to mid-ventricular hypertrophy is also easily demonstrated.

The CMR studies have illustrated the contribution of abnormal mitral subvalvular morphology in LVOT obstruction (20,21) (Fig. 6, Online Video 2). Compared with control subjects, HCM patients have a higher incidence of papillary muscle anomalies such as bifid or multiple accessory papillary muscles, as well as anteroapical papillary muscle displacement that encroaches into the LVOT during systole (19,22). Figure 7 schematically illustrates the common papillary muscle anatomical variations that contribute to LVOT obstruction. During CMR acquisition, careful attention is paid on the short-axis cine images, with additional long-axis cine images specifically planned to demonstrate subvalvular anatomy. This is especially important in patients with dynamic LVOT obstruction without classic asymmetric septal hypertrophy. A 3-dimensional dataset of the LV with high spatial resolution is obtained with a respiratory navigator ECG-gated whole-heart sequence that allows offline multiplanar reconstruction of papillary and subvalvular anatomy.

Although CMR assessment of the LVOT is primarily anatomical, LVOT acceleration and flow turbulence can be diagnosed as systolic signal void in flow-sensitive gradient echo sequences, and LVOT gradient can be quantified with phase contrast flow-sensitive sequences. However, this is often technically challenging in HCM for a variety of reasons. Proper alignment of the imaging plane to obtain the highest flow velocities can be time consuming and prone to errors. Intravoxel dephasing and signal loss due to phase offset errors also make the accurate quantification of turbulent flow difficult. Imaging with provocation and during exercise is also difficult with CMR. New CMR sequences under development might allow the routine 3-dimensional acquisition of the flow pattern and velocities not limited by imaging planes (23), real-time velocity encoding (24), as well as accurate measurement of turbulent jet velocities (25). Until then, echocardiography remains the "gold stan-

ABBREVIATIONS AND ACRONYMS

CMR = cardiac magnetic resonance

ECG = electrocardiography

HCM = hypertrophic cardiomyopathy

ICD = implantable cardioverter defibrillator

LGE = late gadolinium enhancement

LV = left ventricle/ventricular

LVH = left ventricular hypertrophy

LVOT = left ventricular outflow tract

RV = right ventricle/ventricular

SCD = sudden cardiac death

TEE = transesophageal echocardiography

TTE = transthoracic echocardiography

Table 1. Typical Dedicated CMR Study for HCM: Potential Advantages and Limitations

Typical Sequences	Technical Details	Information Obtained	Potential Advantages Over Echocardiography	Limitations of CMR Techniques
Bright blood cine image	Balanced SSFP	Septal thickness	Image quality superior to echocardiography	Availability and portability of echocardiography is unlikely to be matched by CMR
	Optionally, 3D SSFP	Relationship between the septum, mitral valve, and subvalvular apparatus in the LVOT obstruction	No limitation of imaging window and imaging plane	3D cine sequences are currently limited by acquisition time, inferior spatial and temporal resolution
		Global and regional ventricular function	Quantification of ventricular volumes, function, and mass with excellent reproducibility	Functional information on dynamic LVOT obstruction might not be easily obtained
		Ventricular mass	Compared with transesophageal echocardiography, CMR is noninvasive	
LGE images	Phase-sensitive inversion recovery gradient echo sequence	Extent and location of myocardial fibrosis	Tissue characterization for myocardial fibrosis is unique to CMR	Limited role in patients with chronic renal failure due to concern over nephrogenic systemic fibrosis
				Quantification of myocardial fibrosis is time consuming
				Detection of diffuse myocardial fibrosis remains challenging
				Selection of wrong nulling time on LGE might make measurement of myocardial fibrosis inaccurate
3D SSFP whole heart dataset	Respiratory navigator gated ECG gated 3D SSFP sequences	Papillary muscle anatomy	Localization of papillary muscle number, extent, proximal and distal attachments	3D information with a high spatial resolution is not easily obtainable
		Coronary artery anatomy	Exclusion of coronary anomalies as alternative cause of cardiac arrhythmia and SCD	
Tagged cine images	SPAMM sequence	Regional wall deformation	Accurate characterization of regional deformation: strain and strain rate	Data analysis to obtain strain and strain rate remains time consuming
				Limited clinical utility
Flow quantification sequences	Velocity-encoded cine sequences	Aortic flow velocities, profile, and volume	Quantification of flow velocities and volume	Accuracy of flow measurements in HCM has not been validated
		LVOT flow velocities and profile	Quantification of mitral regurgitation	
		Mitral regurgitant volumes and fractions		
Perfusion images—rest	90° saturation recovery pre-pulse followed by gradient echo readout sequences	Myocardial perfusion	Information on myocardial perfusion is easily obtained with CMR, at the time of contrast injection for LGE assessment	Data analysis to quantify myocardial perfusion remains the realm of advanced research laboratory
				Clinical implications of abnormal findings not well-established

3D = 3-dimensional; CMR = cardiac magnetic resonance; ECG = electrocardiography; HCM = hypertrophic cardiomyopathy; LGE = late gadolinium enhancement; LVOT = left ventricular outflow tract; SCD = sudden cardiac death; SPAMM = spatial modulation of magnetization; SSFP = steady state free precession.

dard" for flow quantification of LVOT obstruction in HCM.

CMR assesses mitral regurgitation with diverse techniques. Gauging severity on the basis of turbulence-related signal void in various cine sequences is fraught with errors, because it is highly dependent on pulse sequence parameters. Most commonly, visualizing the regurgitant jet on flow-sensitive gradient echo sequences is complemented with quantification, by subtracting forward aortic flow derived from the velocity-encoded phase contrast sequence, from stroke volume derived from LV volume measurements (26,27). Although CMR also demonstrates mitral leaflet abnormalities, echocardiography remains the test of choice because of superior temporal resolution and various Doppler techniques for hemodynamic information.

Disease characterization: atypical forms of HCM. In the past, it was presumed that HCM is synonymous

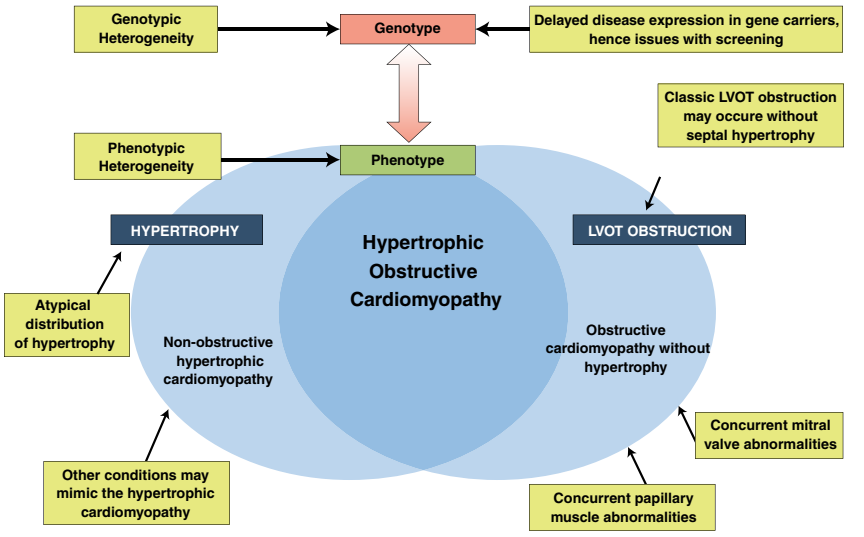

Figure 1. Diagnostic Challenges Faced by Clinicians in Suspected and Established HCM

This figure demonstrates the potential difficulties in diagnosis of hypertrophic cardiomyopathy (HCM) due to phenotypic and genotypic heterogeneity. Patients within the same family might have different phenotypic expressions, ranging from gross hypertrophy with severe left ventricular outflow tract (LVOT) obstruction to minimal hypertrophy and no LVOT obstruction.

with asymmetric septal hypertrophy, and hence a septal to posterior wall ratio >1.3 is diagnostic of HCM (28,29). Subsequent studies, including those with CMR, showed that atypical cases of HCM are more common than previously thought (30,31). These range from diffuse global hypertrophy on 1 end of the spectrum to focal segmental hypertrophy on the other end. The focal hypertrophy variant sometimes involves only 1 to 2 myocardial segments, often with a noncontiguous pattern of hypertrophy where hypertrophied segments are separated by regions of normal thickness (30). Normal LV mass does not exclude

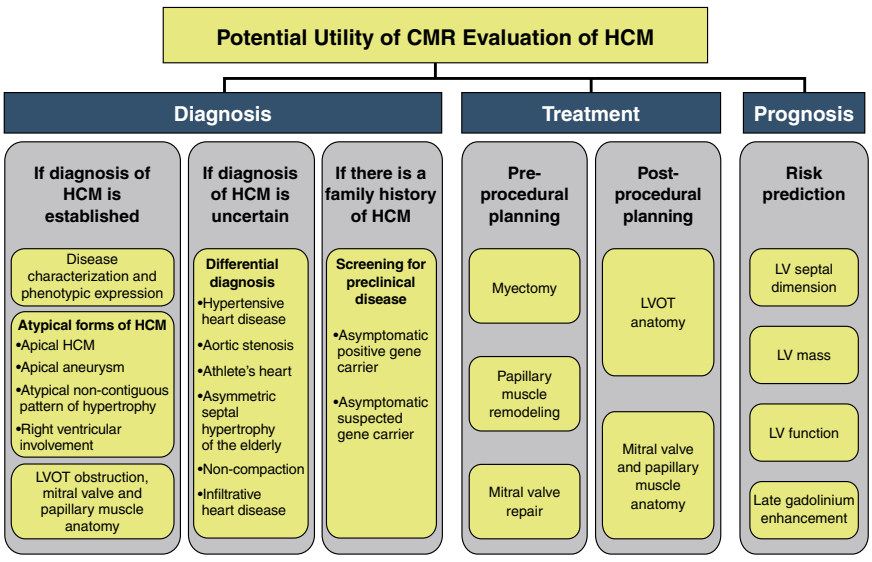

Figure 2. Potential Role of CMR in Management of HCM

This figure explains the potential utility of cardiac magnetic resonance (CMR) in the diagnosis and management of HCM. It has a potential role in establishing the diagnosis, pre-procedural planning, and prognostication. LV = left ventricular; other abbreviations as in Figure 1.

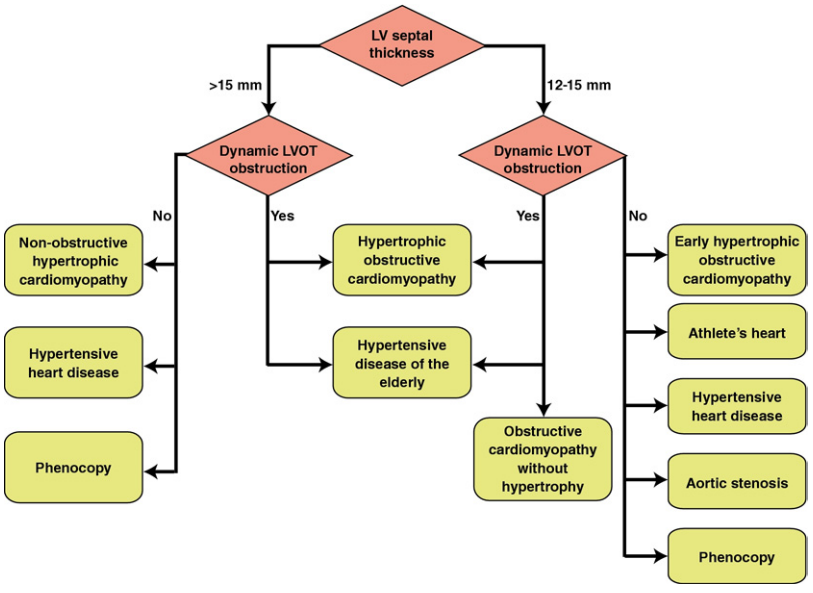

Figure 3. Simplified Approach to the Differential Diagnosis of HCM

This figure is a simplified diagnostic approach in a patient with increased LV thickness. Please note that for such an approach to be successful, multimodality imaging is necessary. Abbreviations as in Figures 1 and 2.

HCM in these patients. Such a focal noncontiguous pattern of hypertrophy is not usually seen in secondary forms of hypertrophy (e.g., hypertension). In 12% of HCM patients, focal segmental LV hypertrophy is limited to the anterolateral free wall, posterior septum, or apex (30,32). These areas are technically challenging for TTE, due to imaging window limitation, and in 1 study, the diagnosis of HCM was missed in 6% of patients by echocardiography (32).

Apical HCM (Fig. 6, Online Video 3) with predominantly LV apical hypertrophy is commonly missed on TTE, because of limited acoustic windows and foreshortening, and CMR has incremental utility here (33). Similarly, apical aneurysm can be missed on noncontrast TTE in 40% of cases and is best visualized on CMR (34). Apical aneurysms present as dyskinesis or akinesis with a thin rim of myocardium, often with transmural scarring on LGE, and are associated with adverse outcomes with an annual event rate of 11%. In addition, recent reports found that HCM patients often have significant right ventricular (RV) involvement with increased RV wall thickness and mass compared with control subjects (35). Assessment of RV by CMR is superior to echocardiography.

Differential diagnosis. Accurate diagnosis of HCM is important, because of the significant lifestyle altering and familial implications.

HYPERTENSIVE HEART DISEASE AND AORTIC STENOSIS. Hypertensive heart disease and aortic stenosis both present with concentric rather than asymmetrical LVH. HCM and hypertensive heart disease occasionally might be difficult to differentiate, but in general, LV wall thickness of hypertensive heart disease is <15 to 16 mm. Specific studies comparing hypertensive heart disease and HCM with CMR are sparse, although with improved image quality, CMR is more sensitive in detecting differences in segmental wall thickness. Interestingly, although myocardial fibrosis on LGE has traditionally been considered rare in hypertensive heart disease and aortic stenosis, a recent study demonstrated patchy LGE in more than 50% of hypertensive heart disease and aortic stenosis patients with significant LVH (36). Another report also suggested a potential prognostic role for LGE in aortic stenosis (37). As such, LGE itself might not be specific for HCM, and its prognostic utility in other disorders needs to be studied further. In addition, in a small group of patients with concomitant valvular aortic stenosis and LVOT obstruction from asymmetric septal hypertrophy, CMR can identify the site of jet turbulence and distinguish the relative contributions of the 2 disease processes.

ATHLETE'S HEART. Athlete's heart is characterized by a mildly enlarged LV cavity, symmetric

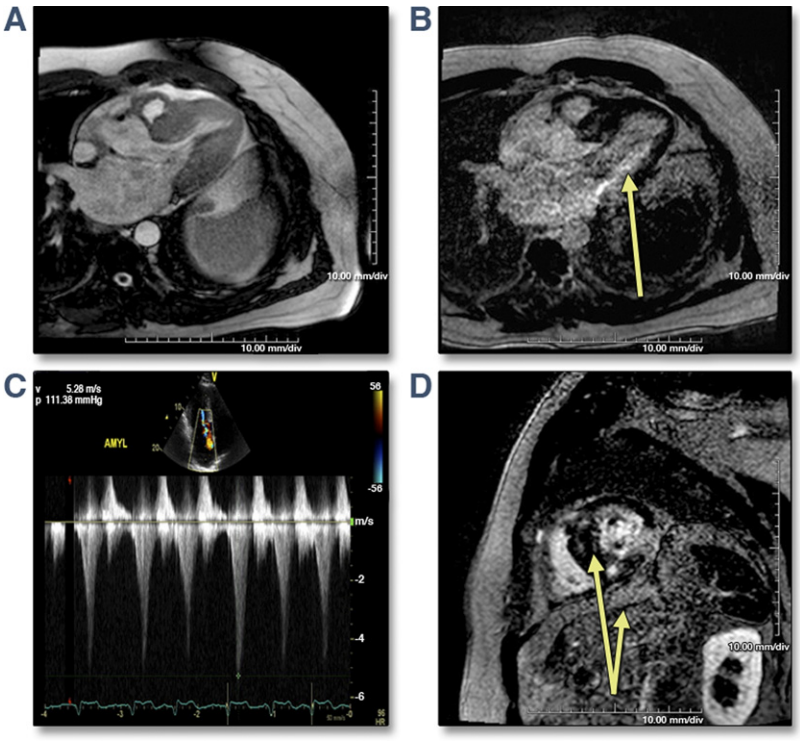

Figure 4. Patient With "Typical" HCM and LVOT Obstruction

(A) Patient with "typical" HCM with marked basal septal hypertrophy on CMR and **(B)** LVOT obstruction **(arrow)** on Doppler echocardiography after amyl nitrite. Patient with "garden-variety" hypertrophic obstructive cardiomyopathy with severe basal septal hypertrophy and LVOT obstruction. Also note the myocardial fibrosis. Late gadolinium enhancement in long-axis **(C)** and short-axis **(D)** views showed myocardial fibrosis **(arrows)**. See Online Video 1. Abbreviations as in Figures 1 and 2.

thickening of the LV wall—typically <15 mm—and normal diastolic function on Doppler echocardiography. CMR complements TTE in this condition, because it accurately measures LV volumes, mass, and function, with high reproducibility (9,38). Researchers used wall thickness indexed to end-diastolic ventricular volume to distinguish athlete's heart from HCM (39). Despite this, such differentiation remains difficult, and some subjects might have to undergo a period of deconditioning to document reverse remodeling as a definitive proof of athlete's heart (40).

NONCOMPACTION. Noncompaction is characterized by prominent LV trabeculations, and differentiation of compacted and noncompacted layers is often difficult in echocardiography, especially without contrast. CMR is ideal for delineating compacted and noncompacted layers. An end-diastolic ratio between noncompacted and compacted layers of more than 2.4:1.0 is a proposed imaging criterion for noncompaction. CMR also precisely delineates the characteristic abrupt transition zone between affected and nonaffected segments as well as diagnoses the commonly associated LV thrombus.

INFILTRATIVE HEART DISEASES. Infiltrative heart diseases mimic HCM with LVH and its functional consequences. CMR plays an important role in excluding these conditions.

Fabry's disease. Fabry's disease is an X-linked recessive glycolipid storage disease with deficient alpha-galactosidase activity. The resulting phenotype is of concentric hypertrophy, with LGE found in 50% of patients, typically in the basal inferolateral segment in a mid-myocardial distribution (41) (Fig. 8, Online Video 4).

Hypereosinophilic syndrome. Hypereosinophilic syndrome presents with apical fibrosis and mural thrombus, frequently leading to apical cavity obliteration, and therefore can sometimes mimic apical HCM on TTE (42). Areas of increased subendocardial signal intensity are often observed.

Sarcoidosis. Sarcoidosis usually presents with a restrictive cardiomyopathy with generalized LV thickening, but asymmetric basal septal involvement can

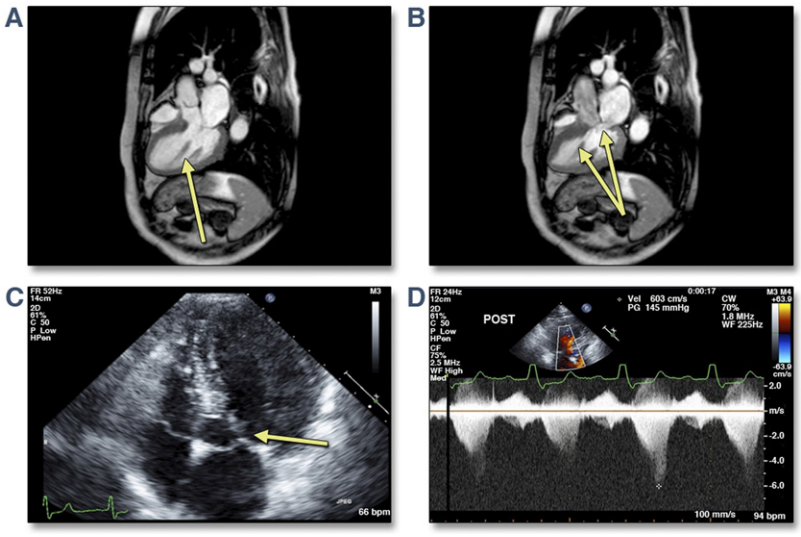

Figure 5. Patient With "Obstructive Cardiomyopathy" With Minimal LVH

The main pathology is the abnormal hypermobile bifid papillary muscle **(arrows, A and B)** resulting in systolic anterior motion of the anterior mitral valve leaflet **(arrow, C)**, seen on CMR (diastole **[A]** and systole **[B]**) and echocardiography **(C)**. This causes severe post exercise LVOT obstruction **(D)**. See Online Videos 1 and 2. LVH = left ventricular hypertrophy; other abbreviations as in Figures 1 and 2.

mimic HCM (43). The LGE pattern is variable, most commonly affecting the basal and lateral segments.

Amyloidosis. Amyloidosis presents with diffuse LV wall thickening and diffuse LGE associated with a characteristic shortening of myocardial nulling time on inversion recovery sequences (44,45) (Fig. 9, Online Video 5).

Screening. Despite advances in gene testing in HCM, mutations are only identified in 60% of index HCM cases (3,4). Phenotypic heterogeneity, incomplete penetrance, and delayed disease presentation sometimes until adulthood also make it challenging to screen for suspected carriers and detect preclinical disease in definite carriers. Current strategy involves a combination of clinical assessment, ECG, and TTE at 12- to 18-month intervals from age 12 to adulthood, although negative clinical and imaging tests cannot fully exclude the risks of future disease development (46).

Although a large prospective study of HCM screening with CMR has not been performed, CMR

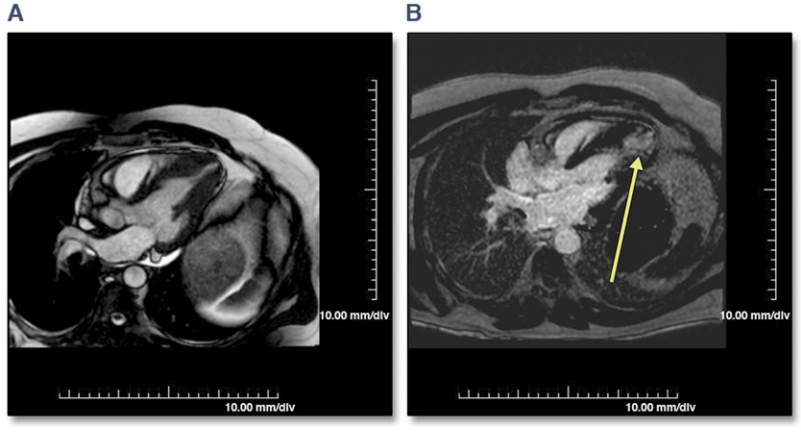

Figure 6. Apical HCM

Apical HCM with marked mid and apical hypertrophy on cine CMR **(A)**. Patchy late gadolinium enhancement **(arrow)** is observed in the hypertrophied apex on late gadolinium enhancement sequences **(B)**. See Online Videos 1 and 3. Abbreviations as in Figures 1 and 2.

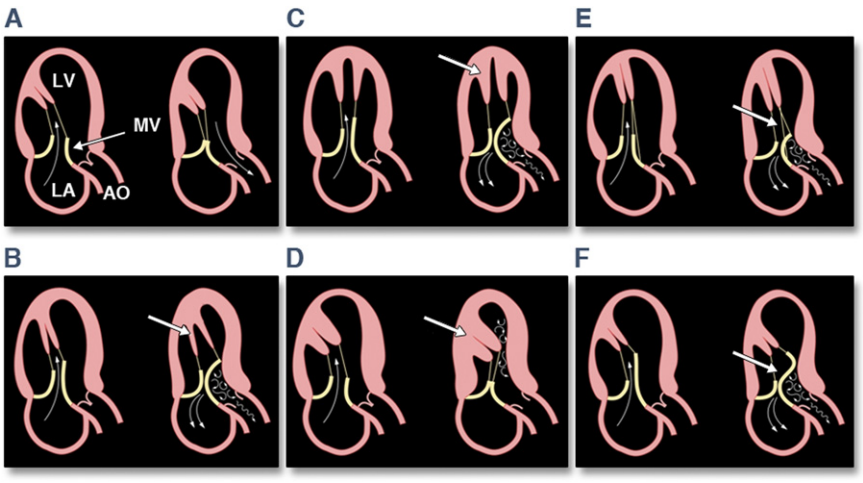

Figure 7. Schematic Diagram of the Common Variations in Papillary Muscle Anatomy in HCM

Schematic diagram of the common variations in papillary muscle anatomy in HCM **(arrows)**. The left image represents the myocardium during diastole, the right image represents systole. **(A)** Normal papillary muscle orientation; **(B)** bifid papillary muscles; **(C)** apical displacement of the papillary muscles; **(D)** hypertrophied papillary muscles with mainly mid-cavity obstruction during systole; **(E)** abnormal chordal attachment to the mid-portion of the mitral valve (MV); and **(F)** elongated anterior MV leaflet. See Online Video 2. Ao = aorta; LA = left atrium; LV = left ventricle; other abbreviation as in Figure 1.

might detect subtle abnormalities and/or serial changes that are otherwise not observed on echocardiography, enabling the detection of pre-clinical disease. In small studies, CMR detected abnormal wall thickening in approximately 20% of asymptomatic gene carriers not appreciated by echocardiography. Pre-hypertrophic crypts in the basal and mid inferoseptum have been suggested as a sign of a mutation carrier (47,48). In a recent study, high levels of serum C-terminal propeptide of type I procollagen were found in subjects with HCM-mutations without LVH, as compared with control subjects (49). Parallel to the research in strain imaging by echocardiography to detect subclinical contractile dysfunction in carriers (50,51), CMR myocardial tagging techniques have also been investigated; however, studies remain sparse (52).

CMR and Treatment Strategies

Symptomatic patients with obstructive HCM intractable to medical therapy can either undergo surgical myectomy or alcohol septal ablation. CMR is an

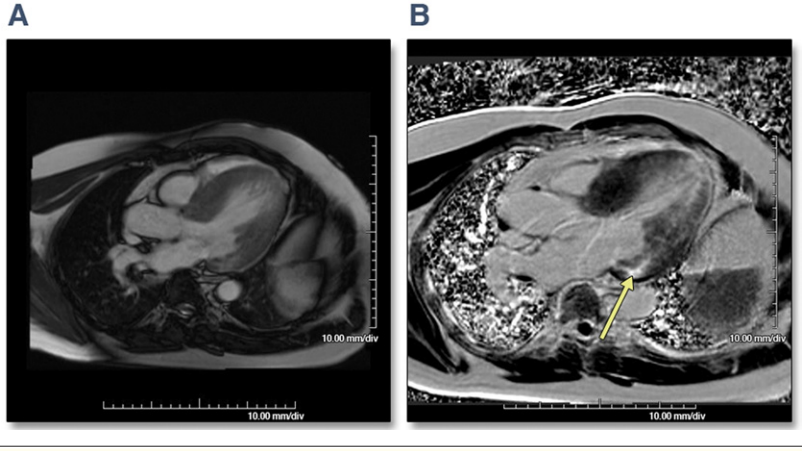

Figure 8. Patient With Fabry's Disease

Cine sequence in the 3-chamber view demonstrates the concentric hypertrophy **(A)**, associated with the basal posterolateral segment **(arrow)** late gadolinium enhancement **(B)**. See Online Video 4.

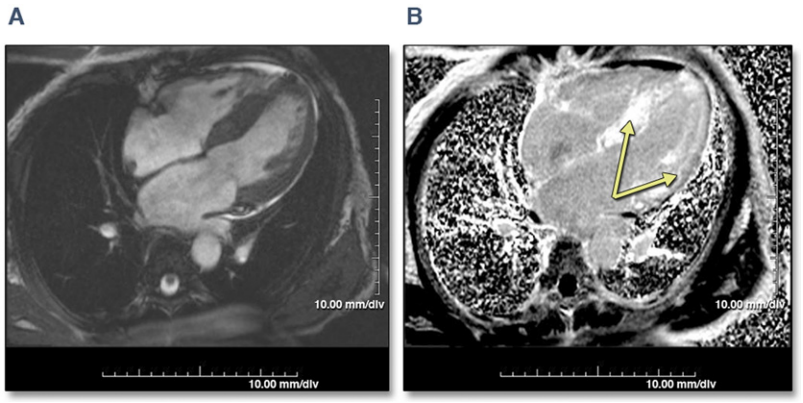

Figure 9. Patient With Cardiac Amyloidosis

Cine sequence in the 4-chamber view demonstrates diffuse concentric left ventricular hypertrophy **(A)**. Late gadolinium enhancement images showed extensive amyloid infiltration **(arrows)** with generalized gadolinium uptake, resulting in high signal intensity and a reduced myocardial nulling time on inversion recovery sequences **(B)**. See Online Video 5.

important adjunct in the pre-procedural planning for both procedures. We perform pre-operative CMR and perioperative TEE to precisely measure the degree and extent of the anteroseptal and inferoseptal hypertrophy as well as the relationship of the septum with the anterior mitral valve leaflet, subvalvular apparatus, and papillary muscle morphology. Accurate pre-operative anatomical assessment of the subvalvular anatomy has led to the increasing recognition that septal myectomy might need to be combined with mitral valve and chordae remodeling and/or papillary muscle reorientation to optimally relieve LVOT obstruction (53,54).

CMR is extensively used to assess the effectiveness of alcohol septal ablation (55,56). CMR after surgical myectomy or alcohol septal ablation provides insights on the effect of the respective procedures on the interventricular septum (55). Surgical myectomy predictably leads to a discrete resected area in the anteroseptum, whereas alcohol septal ablation leads to a variable pattern of myocardial scar, usually inferiorly in the basal septum with extension to the RV side of the septum. The improvement of LVOT obstruction is also more variable after alcohol septal ablation.

CMR and Prognosis

LGE. There is a growing body of published reports on the role of LGE on CMR in HCM risk stratification, but a large prospective study on how the data should be interpreted to alter management is still lacking. The histological correlate of LGE in HCM seems to be increased myocardial collagen rather than myocardial disarray, which is also observed on histological specimens. Increased myocardial collagen is postulated to reflect microvascular ischemia and microscopic replacement fibrosis due to small intramural coronary arteriole dysplasia (57,58). The latter finding correlates with LGE in myectomy specimens from patients who underwent surgery for LVOT obstruction (58). An alternative hypothesis for LGE in HCM suggested that the causative sarcomeric gene mutations might lead to a phenotypic expression of increased myocardial connective tissue deposition (59).

The prevalence of LGE is variable in different cohorts. In those with manifest HCM, it varies between 40% and 80% (10–14,60). The commonly found LGE pattern is patchy, multifoci midmyocardial fibrosis, especially in regions of hypertrophy (Figs. 4B, 4D, and 6B). Other observed patterns include diffuse confluent transmural septal fibrosis and patchy septal fibrosis at RV insertion points.

LGE correlates with LV wall thickening (10,61) and inversely correlates with LV ejection fraction (61–63). It also correlates with other known clinical markers of SCD (64). The association between LGE and the detection of ventricular arrhythmia on Holter monitoring suggests the potential pathophysiologic link between HCM, myocardial fibrosis, arrhythmia, and ultimately SCD (10–14,60). Recent longitudinal studies suggest a strong association between LGE and SCD (Table 2) (12–14). LGE shows prom-

Table 2. Summary of the Recent Prognostic Studies on the Role of LGE in HCM

	O'Hanlon et al. (13)	Bruder et al. (14)	Rubinshtein et al. (12)
N (% women)	217 (29)	243 (39)	424 (41)
Follow-up, yrs	3.1	3.0	3.6
Clinical (%)			
NYHA functional class III/IV	14	8	53
Wall thickness >30 mm	6	4	7
History of syncope	16	6	16
History of sustained VT/VF	3	6	10
CMR			
Prevalence of LGE (%)	63	61	56
Quantification of LGE	FWHM	2 SD	Qualitative manual tracing
Outcome			
Primary endpoint: LGE vs. no LGE	Primary combined endpoint (25% vs. 7%); HR 3.37 Cardiovascular deaths (5.9% vs. 1.2%); HR 4.45	LGE is associated with all-cause mortality (OR: 5.47) and cardiac mortality (OR: 8.01)	SCD and appropriate ICD discharge (3.4% vs. 0.0%)

FWHM = full-width at half maximum; HR = hazard ratio; ICD = implantable cardioverter defibrillator; NYHA = New York heart association; OR = odds ratio; VF = ventricular fibrillation; VT = ventricular tachycardia; other abbreviations as in Table 1.

ise, but there is insufficient evidence for inserting an ICD on the basis of LGE alone. Further studies should establish the role of LGE in identifying high-risk patients from among those who are currently classified as intermediate-risk with clinical criteria and do not otherwise qualify for ICD insertion.

Certain aspects of LGE in HCM prognostication are technically challenging and worthy of mention. Error in the appropriate myocardial nulling time might over- or underestimate true fibrosis burden. The use of phase sensitive inversion recovery sequences has greatly improved this aspect (65). Although LGE is assessed qualitatively in routine clinical practice, LGE in relation to overall LV myocardial volume can be quantified with automated software. Various methods exist and most commonly calculate the total areas of signal intensity above a certain number of SDs (n = 2 to 6) over that of the mean signal intensity of nulled myocardium (61,66–68). These differences in methodology translate into differences in the quantified area of LGE and potentially impact on the ability to generalize individual research studies. The current assessment of myocardial fibrosis contrasts areas of LGE with areas of presumed "normal" nulled myocardium. Histological studies, however, suggest a global increase in myocardial fibrosis that current LGE imaging techniques cannot detect. New techniques such as T1 mapping (69) and equilibrium contrast CMR (70) might offer alternatives to quantify the overall extent of myocardial fibrosis.

With respect to LGE and prognosis, the relative importance of the severity, extent, and location of LGE as well as whether there is a threshold effect below which fibrosis does not impact on prognosis is uncertain.

Septal thickness and LV mass. The current guidelines include LV thickness >30 mm on TTE as an important prognostic criterion (6). The improved accuracy of CMR in measuring LV thickness will likely refine this. In addition, CMR provides accurate and reproducible information on overall LV mass. Investigators have studied the relative prognostic value of LV wall thickness and mass by CMR. HCM patients typically have a "thickness-mass" mismatch because of the differing extent of hypertrophy in individual LV segments. It was found that LV mass indexed to body surface area above 2 SDs of a healthy control cohort is a sensitive but not specific predictor of outcome, whereas an LV wall thickness >30 mm is a more specific but less sensitive predictor (71). Future studies will clarify how best to use this information in management.

New Developments in CMR Imaging of HCM

Several new developments in CMR imaging of HCM are worth discussing, but their clinical applications remain undecided.

There has been increasing awareness of the importance of ventricular vascular interactions in various cardiac disorders. HCM patients were

found to have a higher pulse wave velocity than matched control subjects, indicating increased aortic stiffness (72). This was independently associated with lower peak oxygen consumption on cardiopulmonary exercise testing (73). Whole-heart CMR sequences also provided insight that HCM patients have a steep angle between the aortic root and the LV long axis, compared with control subjects. The acuteness of this LV-aortic root angle correlates with age and the observed LVOT gradient (74). These early findings highlight the potential impact HCM has on the aortic vasculature and the usefulness of CMR in investigating this relationship.

CMR perfusion studies in HCM investigated the role of microvascular dysfunction in intramural coronary arteriole dysplasia and subsequently myocardial fibrosis as well as in blunting myocardial blood flow during vasodilator stress, which has been observed in HCM, especially subendocardially (75). Furthermore, CMR spectroscopy with 31-phosphorus demonstrated an altered myocardial energy metabolic profile in HCM that correlated with the severity of LGE (76). With CMR spectroscopy, perhexiline, a modulator of substrate metabolism, was shown to ameliorate cardiac energetic impairment, correct diastolic dysfunction, and increase exercise capacity in symptomatic HCM patients (77).

Myocardial tagging quantifies myocardial mechanics parameters such as strain, strain rate, and torsion and has been studied in HCM. Not unexpectedly, strain is reduced in hypertrophied myocardial segments and is inversely related to severity (52,78). These findings are analogous to strain measured by speckle tracking on echocardiography, where impaired longitudinal strain was shown to correlate with fibrosis severity (79).

Conclusions

HCM is a heterogeneous disease with complex morphological expression that requires accurate disease characterization for optimal therapeutic planning and risk-stratification. CMR has emerged as a useful adjunct for these purposes. With the increasing incorporation of multimodality imaging in the clinical assessment of HCM, our understanding of the significance of subtle morphological differences will continue to grow, and further research will define new prognostic markers and improve current treatment strategies.

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Key Words: cardiac magnetic resonance ■ hypertrophic cardiomyopathy ■ late gadolinium enhancement.

APPENDIX

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